Metastatic Hormone-Sensitive Prostate Cancer: Toward an Era of Adaptive and Personalized Treatment

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Overview

The advent of more effective treatment combinations for metastatic hormone-sensitive prostate cancer (mHSPC) has been built on successes in therapy development for metastatic, castration-resistant prostate cancer (mCRPC). Both disease phases hold similar challenges and questions. Is there an optimal therapy sequence to maximize disease control and balance treatment burden? Are there clinical and biologically based subgroups that inform personalized and/or adaptive strategies? How can clinicians interpret data from clinical trials in the context of rapidly evolving technologies? Herein, we review the contemporary landscape of treatment for mHSPC, including disease subgroups informing both intensification and potential deintensification strategies. Furthermore, we provide current insights into the complex biology of mHSPC and discuss the potential clinical application of biomarkers to guide therapy selection and the development of novel personalized approaches.

INTRODUCTION

Prostate cancer is among the most common solid malignancies in men, accounting for a significant proportion of the global burden of cancer morbidity and mortality.[1] The diagnosis and clinical presentation of prostate cancer may be influenced by sociodemographic, geographic, economic, and biological factors. Most men in developed nations are diagnosed when cancer is confined to the prostate gland, and this has stemmed, historically, from the advent and widespread use of prostate-specific antigen (PSA) screening.[2] Despite variation in the mode and stage of diagnosis, the spectrum of disease can be consistently divided by two key clinical factors: (1) the presence or absence of metastasis on conventional imaging modalities and (2) sensitivity or resistance to gonadal testosterone suppression (TS). The former is determined by clinical and radiographic evaluation and remains an area of rapid evolution in recent times with the adoption of novel diagnostic imaging techniques, such as magnetic resonance imaging and positron emission tomography (PET). The latter provides a phenotypic label in relation to response to androgen deprivation therapy (ADT)—the backbone of systemic therapy for metastatic prostate cancer—and has a formalized definition, most notably by the Prostate Cancer Working Group.[3]

The incidence of mHSPC is increasing.[4,5] US-based studies point to shifts in stage of diagnosis, which parallel changes in PSA screening recommendations by the US Preventative Services Task Force.[6] Although not inferring direct causality, the rising incidence of metastatic prostate cancer is considered a high priority because of the incurable nature of advanced disease associated with inevitable therapy resistance and worse survival. Treatment for mHSPC has evolved considerably over the past decade because of successive large, randomized, phase III clinical trials demonstrating improvements in overall survival (OS) and quality of life (QoL) with combination therapy above the historical standard of ADT alone (Table 1). Many of the novel strategies for mHSPC have arisen from therapies proven successful in mCRPC (Fig 1). We have been ushered into a new era of mHSPC, which has led to intense questioning of how we can both balance and improve the benefit, burden, and precision of treatment for patients.

TREATMENT OF mHSPC

Inhibition of the androgen receptor (AR) remains the mainstay of treatment for mHSPC, owing to seminal experiments published in 1941, which proved that prostate cancer is an androgen-driven and androgen-dependent disease that responds to testosterone deprivation.[17] These discoveries led to Charles Huggins receiving the Nobel Prize in Physiology or Medicine in 1966. Indeed, androgen signaling is central in driving growth and survival of prostate cancer even in treatment-resistant states.[18] TS was

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PRACTICAL APPLICATIONS

- The landscape of treatment for metastatic hormone-sensitive prostate cancer (mHSPC) continues to evolve, with a shift to combination systemic therapy being established as the backbone of contemporary treatment.
- Clinical factors, including disease volume and presentation, demonstrate prognostic associations and have been studied in the context of predicting the benefit of combination strategies, including triplet systemic therapy.
- The role of treatment intensity modulation is of high interest, given that modern trials in mHSPC have demonstrated that a subset of patients have favorable long-term outcomes. Deintensification strategies guided by prostate-specific antigen response aim to balance both the benefits and long-term risks and burden of treatment.
- Biomarker development in mHSPC is leveraging the rapid accumulation of knowledge from biological profiling of both localized prostate cancer and metastatic, castration-resistant prostate cancer.
- In the era of precision cancer care, targeted novel therapies are being tested in ongoing clinical trials to further personalize therapy for mHSPC.

originally instituted by surgical castration (bilateral orchiectomy), followed by diethylstilbestrol and subsequent development of luteinizing hormone-releasing hormone (LHRH) agonists and antagonists built on the elucidation of hypothalamic pituitary control of gonadal testosterone production. Labrie et al[19] initially hypothesized that the concomitant administration of an antiandrogen to ADT, or complete androgen blockade, eliminates the activity of testicular and adrenal androgens. Early-generation AR inhibitors, such as flutamide, bicalutamide, nilutamide, and cyproterone acetate, are generally not used as monotherapy and instead are more often combined with TS (termed combined ADT) for prevention of flare responses due to initial agonistic (positive feedback) effects of LHRH agonist therapy. An individual patient data (IPD) meta-analysis of 8,275 men from 27 randomized trials comparing TS alone versus combined ADT[20] showed that 5-year OS was improved with nonsteroidal antiandrogens (absolute benefit 3%; two-sided $P = .005$) and possibly worse with cyproterone acetate (absolute reduction 3%; two-sided $P = .04$), compared with TS alone. These data have laid the basis of combined ADT of TS plus weak, early-generation AR inhibitors as a potential control arm in clinical trials of mHSPC. However, real-world practice remains heterogeneous.

ADT Plus Docetaxel or Novel AR Signaling Inhibitor: Doublet Systemic Therapy

ADT plus docetaxel. From the early 1940s to 2015, TS alone with or without an AR inhibitor was a standard treatment for mHSPC before development of castration resistance. In 2004, the TAX 327 and SWOG9916 trials demonstrated a significant improvement in OS for men with mCRPC treated with ADT plus docetaxel/prednisone (or docetaxel plus estramustine in SWOG9916), compared with ADT plus mitoxantrone/prednisone.[21,22] These findings led to an immediate shift in the treatment paradigm of mCRPC. The combination of hormonal therapy and cytotoxic therapy also reflected a strong scientific rationale as clonal populations in advanced and resistant prostate cancer are diverse (both within and between metastases) and may be differentially driven by AR-dependent and non–AR-dependent mechanisms.[23]

Therapy intensification with ADT plus docetaxel in frontline management of mHSPC was tested in three key phase III trials. GETUG-AFU 15 randomly assigned 385 men to either ADT plus docetaxel once every 3 weeks (up to nine cycles, without prednisone) or ADT alone. At a median follow-up of 50 months, OS was not significantly different between the groups (hazard ratio [HR], 1.01; 95% CI, 0.75 to 1.36).[24] Long-term follow-up, at a median of 83.9 months, again failed to show a significant difference in OS; however, post hoc analysis by volume of metastatic disease demonstrated a trend to benefit in the high-volume subgroup (HR, 0.78; 95% CI, 0.56 to 1.09), which did not meet statistical significance and was notably underpowered.[25] The CHAARTED trial was the first to report a significant OS improvement with ADT plus docetaxel for mHSPC—also the first of any combination strategy.[26] In total, 790 men were randomly assigned to ADT alone or ADT plus docetaxel (for six cycles), with a primary end point of OS. The trial had several prespecified stratification factors including disease volume (high versus low), where high-volume was defined as the presence of any visceral metastases, or four or more bone lesions with at least one beyond the vertebral bodies and pelvis. After a median follow-up of 28.9 months, chemohormonal therapy was associated with significantly prolonged OS (57.6 months *v* 44 months, HR, 0.61; 95% CI, 0.47 to 0.80; $P < .001$), as well as improvements in secondary end points including time to CRPC and the proportion of patients with suppressed PSA (<0.2 ng/mL) at 12 months. The effect of docetaxel was particularly pronounced in the high-volume subgroup (65% of cohort). In long-term follow-up, the median OS for patients with high-volume disease was 51.2 months versus 34.4 months (HR, 0.63; 95% CI, 0.50 to 0.79; $P < .001$) for ADT plus

TABLE 1. Summary Data of Completed Trials in Metastatic Hormone-Sensitive Prostate Cancer

Doublet Systemic Therapy

Trial	Patients Enrolled	Intervention Arm	Control Arm	Previous/ Concurrent Docetaxel	Median Follow-Up (months)	Median OS in Intervention Arm (months)	Median OS in Control Arm (months)	Group: HR (95% CI)	*P*
CHAARTED[7]	790	ADT plus docetaxel	ADT	Not allowed	53.7	57.6	47.2	0.72 (0.59 to 0.89)	.0018
STAMPEDE (M1 subgroup)[8]	1,086	ADT plus docetaxel	ADT	Not allowed	78.2	59.1	43.1	0.81 (0.69 to 0.95)	.003
LATITUDE[10]	1,199	ADT plus abiraterone plus prednisone	ADT plus placebo	Not allowed	51.8	53.3	36.5	0.66 (0.56 to 0.78)	<.0001
STAMPEDE[9]	1,917	ADT plus abiraterone plus prednisone	ADT	Not allowed	40	NR	NR	Overall: 0.63 (0.52 to 0.76) M1 subgroup: 0.61 (0.49 to 0.75)	<.001 (overall)
ENZAMET[16]	1,125	ADT plus enzalutamide	ADT plus NSAA	Allowed (concurrent, 45%)	68	NR	NR	Overall: 0.70 (0.58 to 0.84) Early docetaxel: 0.82 (0.63 to 1.06) No early docetaxel: 0.60 (0.47 to 0.78)	<.0001 (overall)
ARCHES[11]	1,150	ADT plus enzalutamide	ADT plus placebo	Allowed (previous, 18%)	44.6	NR	NR	Overall: 0.66 (0.53 to 0.81) Previous docetaxel: 0.74 (0.46 to 1.20) No previous docetaxel: 0.64 (0.51 to 0.81)	<.001 (overall)
TITAN[12]	1,052	ADT plus apalutamide	ADT plus placebo	Allowed (previous, 11%)	44	NR	52.2	Overall: 0.65 (0.53 to 0.79) Previous docetaxel: 1.12 (0.59 to 2.12) No previous docetaxel: 0.61 (0.50 to 0.76)	<.0001 (overall)

Triplet Systemic Therapy

Trial	Patients Enrolled	Intervention Arm	Control Arm	% Synchronous	% High-Volume	Median Follow-Up (months)	Median OS in Intervention Arm (months)	Median OS in Control Arm (months)	Group: HR (95% CI)
ARASENS[13,14]	1,306	ADT plus docetaxel plus darolutamide	ADT plus docetaxel plus placebo	86	77	43.7	NR	48.9	Overall: 0.68 (0.57 to 0.80) Synchronous + HV: 0.69 (0.57 to 0.85) Synchronous + LV: 0.75 (0.45 to 1.27) Metachronous + HV: 0.69 (0.39 to 1.24) Metachronous + LV: NA
PEACE-1 (docetaxel subgroup)[15]	710	SOC plus abiraterone (with or without RT)	SOC (with or without RT)	100	64	45.6	NR	53.2	Overall (all synchronous): 0.75 (0.59 to 0.95)
ENZAMET (docetaxel subgroup)[16]	503	ADT plus docetaxel plus enzalutamide	ADT plus docetaxel plus NSAA	72	71	68 (overall cohort)	Not reported	Not reported	Synchronous (all): 0.73 (0.55 to 0.99) Synchronous + HV: 0.79 (0.57 to 1.10) Synchronous + LV: 0.57 (0.29 to 1.12) Metachronous (all): 1.10 (0.65 to 1.86)

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; HV, high-volume; LV, low-volume; NA, not applicable; NR, not reached; OS, overall survival; RT, radiotherapy; SOC, standard of care.

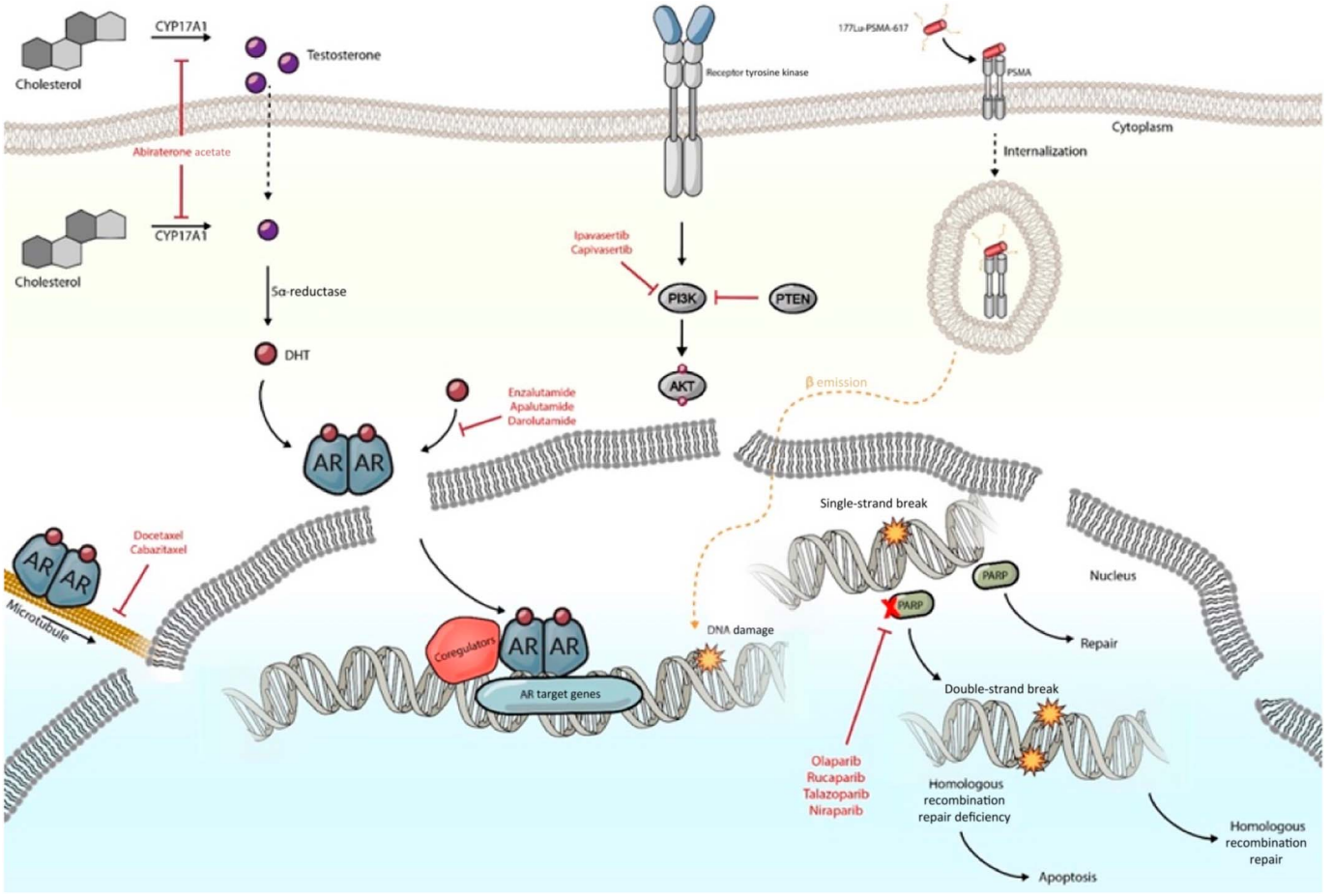

FIG 1. Therapeutic targets of systemic therapies for advanced prostate cancer. AKT, AKR thymoma; AR, androgen receptor; CYP17A1, cytochrome P450 17A1; DHT, dihydrotestosterone; PARP, poly (ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tensin homolog.

docetaxel versus ADT alone, respectively.[7] Notably, no significant OS benefit was observed for patients with low-volume disease (HR, 1.04; 95% CI, 0.70 to 1.55; $P = .86$), suggesting marked heterogeneity of effect. Subsequent meta-analysis of aggregate data from GETUG-AFU 15 and CHAARTED with harmonized disease volume definitions confirmed heterogeneity in effect sizes between volume subgroups, with significant OS advantage from docetaxel demonstrated in high-volume disease (synchronous and metachronous), modest OS benefit in synchronous low-volume disease, and no OS benefit in metachronous, low-volume disease.[27] The multiarm, multistage STAMPEDE trial also showed a significant benefit for addition of docetaxel to ADT for mHSPC.[28] In a trial population of 2,962 men, which also included patients with high-risk localized disease (39%), arm C (ADT plus docetaxel) and arm E (ADT plus docetaxel plus zoledronic acid) demonstrated improved OS compared with ADT alone (HR, 0.78; 95% CI, 0.66 to 0.93; $P = .006$ and HR, 0.82; 95% CI, 0.69 to 0.97; $P = .022$, respectively). Subgroup analysis showed this effect clearly in men with metastatic disease. Updated analysis of this subgroup at a median follow-up of 78.2 months failed to show heterogeneity of docetaxel effect on OS by retrospectively evaluated metastatic burden (per CHAARTED definition).[8] Notably, 95% of the patients in the STAMPEDE-M1 cohort had synchronous disease. The latter clearly differed to the patient mix of CHAARTED and GETUG-15, which had 17% of patients with metachronous, low-volume disease. An IPD meta-analysis of 2,261 men from GETUG-AFU 15, CHAARTED, and STAMPEDE by the STOPCAP group demonstrated a gradient effect of OS benefit for the addition of docetaxel to ADT, with the most pronounced effect in the synchronous, high-volume subgroup. A modest effect was noted in the metachronous, high-volume subgroup and synchronous, low-volume subgroup. No effect was seen in metachronous, low-volume disease, which is associated with a more favorable prognosis with TS alone.[29] It should also be noted that not all patients are fit for docetaxel, often because of comorbid conditions. Radiation to the prostate also has an

OS benefit with a more favorable adverse event profile than docetaxel for men with synchronous, low-volume mHSPC.[30]

The role of prostate RT. Treatment of the primary tumor in the face of metastatic disease is an enticing concept with the rationale of eliminating a significant source of lethal metastatic seeding. Between 2013 and 2016, STAMPEDE addressed this strategy in mHSPC, randomly assigning 2,061 men to the standard care arm (ADT, with concurrent docetaxel permitted from late 2015) or standard care plus prostate radiotherapy (RT) delivered over 4-6 weeks.[31] Fifty-four percent of men had high metastatic burden, and 18% received up-front docetaxel. The addition of prostate RT significantly improved failure-free survival, but not OS (HR, 0.92; 95% CI, 0.80 to 1.06; $P = .226$) in the overall cohort. However, there was a pronounced OS benefit in patients with low metastatic burden (HR, 0.68; 95% CI, 0.52 to 0.90; $P = .007$), which was not evident in high-burden disease (interaction $P = .01$). This differential effect was again observed in long-term follow-up, and there was no evidence of deterioration in global QoL and long-term high-grade urinary toxicity.[32] When combined with data from the smaller HORRAD trial, meta-analysis by the number of bone metastases demonstrated significant benefit for patients with <5 bone lesions and not higher burden disease.[30] On the basis of these data, prostate RT is an established standard for synchronous, low-burden/volume mHSPC; however, questions remain regarding its role with combination systemic therapy. The proportion of patients treated with docetaxel in the STAMPEDE radiation cohort does not allow for clear conclusions to be drawn from the subset of patients with low-burden disease treated with chemohormonal therapy. PEACE-1 has similar subgroups that may be pooled for analysis and will also define the role of prostate RT combined with ADT plus abiraterone (with or without docetaxel).

ADT plus AR signaling inhibitor. After the proven OS-prolonging benefit of AR signaling inhibitors (ARSIs) in CRPC, several phase III, randomized trials have cemented the role of intense ADT, with a combination of TS plus ARSI, for mHSPC.

Abiraterone acetate, which decreases androgen synthesis by inhibiting CYP17A1, has been evaluated in the STAMPEDE, LATITUDE, and PEACE-1 trials. STAMPEDE assigned men with HSPC 1:1 to either ADT plus abiraterone plus prednisolone (arm G) or ADT alone.[9] Fifty-two percent of men had metastatic disease. At a median follow-up of 40 months, a significant improvement in the primary end point of OS was noted, with a magnitude of effect in the metastatic subgroup, again 95% with synchronous disease, strikingly similar to the aforementioned docetaxel trials (HR, 0.61; 95% CI, 0.49 to 0.75). The clinically meaningful secondary end point of time to symptomatic skeletal events was also significantly improved with combination therapy. LATITUDE randomly assigned 1,199 men to analogous treatment arms; however, the cohort of patients with mHSPC were selected specifically for poor prognostic features—all patients had synchronous metastatic disease and at least two of Gleason score ≥8, ≥3 bone lesions, and presence of visceral metastasis.[33] ADT plus abiraterone significantly improved OS at a planned interim analysis (HR, 0.62; 95% CI, 0.51 to 0.76; $P < .0001$). Time to pain progression, initiation of chemotherapy, and symptomatic skeletal events were all in favor of the abiraterone arm. At the final analysis after a median follow-up of 51.8 months, survival benefit remained (median 53.5 months *v* 36.5 months, HR, 0.66; 95% CI, 0.56 to 0.78; $P < .0001$).[10]

Three next-generation AR inhibitors (enzalutamide, apalutamide, and darolutamide) have established efficacy in mHSPC. ENZAMET[34] and ARCHES[35] tested the addition of enzalutamide to ADT, with the notable difference that the control arm of ENZAMET required patients to receive ADT plus a nonsteroidal antiandrogen. In ENZAMET, concurrent use of up-front docetaxel (maximum six cycles) was permitted after a protocol amendment early in accrual. A total of 1,125 men were randomly assigned, and after a median follow-up of 34 months, clear OS prolongation with enzalutamide was observed (HR, 0.67; 95% CI, 0.52 to 0.86, $P = .002$). Benefit was observed across stratified subgroups, including disease volume (high/low) and metastatic timing (synchronous/metachronous). The primary end point of ARCHES was radiographic progression-free survival (rPFS), and the study design allowed for previous lead-in docetaxel. The enzalutamide arm had significantly longer rPFS (HR, 0.39; 95% CI, 0.30 to 0.50; $P < .001$). In the final analysis after a median follow-up of 44.6 months, a significant OS benefit for ADT plus enzalutamide (HR, 0.66; 95% CI, 0.53 to 0.81; $P < .001$) was confirmed[11]—similar to effect size in ENZAMET. Apalutamide was evaluated in the TITAN trial, which compared ADT plus apalutamide with ADT alone with coprimary end points of radiographic PFS and OS.[36] High-volume disease comprised 62.7% of the cohort, and a small proportion of patients had received previous docetaxel (10.7%). At the first interim analysis, OS was superior in the apalutamide arm (HR, 0.67; 95% CI, 0.51 to 0.89; $P = .005$), and the frequency of high-grade adverse events was similar between treatment arms. Benefit was observed across subgroups, irrespective of timing or volume of metastatic disease. On the basis of these results, the study cohort was unblinded and crossover permitted. Despite 40% of placebo-treated men crossing over to apalutamide, the effect on OS persisted in long-term follow-up.[12]

ADT Plus Docetaxel Plus ARSI: Triplet Systemic Therapy

Identification of patients who benefit from highly intensified up-front systemic therapy is critical. This group of patients is hypothesized to be at risk of greatest symptom burden,

quicker progression to castration resistance, and early death. Moreover, curtailing potential toxicities (including personal financial and economic burden) of multiple therapies in patients unlikely to benefit from this approach is of high priority. There is ongoing debate regarding the role of so-called triplet systemic therapy (ADT plus docetaxel plus ARSI) for mHSPC, given the expanse of different agents in varying combination across the trials reported to date. There are several informative data sets to highlight (Table 1).

First, the role of darolutamide for mHSPC was tested in the ARASENS trial.[13] This randomized, phase III trial assigned 1,306 patients to darolutamide or placebo, both with a mandated backbone of ADT plus docetaxel for all—unique among reported mHSPC studies. Notably, disease volume was not a stratification factor, and most patients (86%) had synchronous metastatic disease. Addition of darolutamide led to significant improvement in OS (HR, 0.68; 95% CI, 0.57 to 0.80; $P < .001$) and similar benefits in prolonging time to pain progression, symptomatic skeletal events, and initiation of chemotherapy, compared with those receiving ADT plus docetaxel. In a post hoc analysis, adding darolutamide to docetaxel and TS clearly improved OS in patients with the high- but not low-volume disease (as defined by CHAARTED criteria) and clear evidence of benefit was seen in patients with high- and low-risk disease (as defined by LATITUDE criteria).[14]

Second, the European PEACE-1 trial evaluated the efficacy of adding abiraterone plus prednisone to ADT, with or without RT, for synchronous mHSPC using a 2×2 factorial design.[15] In a pooled analysis (because of noted noninteraction between abiraterone and RT), men who received abiraterone had significantly longer OS (HR, 0.82; 95.1% CI, 0.69 to 0.98; $P = .03$) compared with ADT control. Across all studies, the rate of high-grade adverse events was higher in abiraterone arms, with common toxicities of hypertension, hypokalemia, and mild transaminase rise.[15] A planned subgroup analysis of PEACE-1 showed significant prolongation of OS with abiraterone among 710 men who received ADT plus docetaxel (HR, 0.75; 95.1% CI, 0.59 to 0.95; $P = .017$). This effect was significant among men with high-volume disease within this subgroup (median OS: 5.14 years *v* 3.47 years, HR, 0.72; 95.1% CI, 0.55 to 0.95; $P = .019$); OS is immature for the low-volume comparison.[15]

Third, ENZAMET allowed for concurrent docetaxel (planned for 45% of patients at investigator discretion), and 85% of patients in the control arm received any subsequent therapy, including 76% who received abiraterone or enzalutamide on progression. A prespecified analysis showed evidence of a difference in OS favoring the enzalutamide arm in the subset of 362 men with synchronous metastatic disease planned for docetaxel (5-year OS: 60% *v* 52%, HR, 0.73; 95% CI, 0.55 to 0.99).[16] This was not evident in patients with metachronous disease planned for docetaxel (HR, 1.10; 95% CI, 0.65 to 186). Within the synchronous population planned for docetaxel, OS point estimates favored enzalutamide in both high- and low-volume subgroups. Curiously, examination of survival curves revealed higher OS rates in the first 30 months for participants receiving enzalutamide plus docetaxel plus TS versus those contemporaneously accrued to enzalutamide plus TS in the highest-risk subgroup (synchronous, high-volume), suggesting the need for early chemotherapy in rapidly lethal disease.

In summary, the collective data support the role of adding an ARSI to those initiating ADT plus docetaxel, particularly for patients with synchronous, high-volume metastatic disease. Further follow-up may more clearly elucidate the role of ADT plus docetaxel therapy in other clinical subgroups. Specifically, the benefit of adding docetaxel to a backbone of ADT plus ARSI is yet unknown; to our knowledge, no randomized trials have reported the outcomes of patients treated with ADT plus ARSI with or without docetaxel. However, exploratory analysis of ENZAMET does highlight the potential of this approach in high-risk subgroups who were chosen for docetaxel and have worse prostate cancer–specific survival.

Baseline Clinical Prognostic Factors

Clinical features at mHSPC diagnosis that associate with survival have largely centered on timing of metastatic disease and volume of disease. In the CHAARTED trial, men with metachronous and low-volume disease had the best prognosis, with a median OS of nearly 70 months with TS and TS plus docetaxel. This contrasted strongly with the synchronous, high-volume subgroup (median OS: 33-48 months) and those with one risk factor falling between those extremes[7]—a stratification also observed in a retrospective registry cohort with aligned definitions.[37] Post hoc analysis of the STAMPEDE-Docetaxel metastatic cohort confirmed the clear prognostic effect of disease volume.[8] IPD meta-analysis of GETUG-AFU 15, STAMPEDE-Docetaxel, and CHAARTED has highlighted, in aggregate, the favorable long-term outcomes of men with metachronous, low-volume disease (5-year OS: 73%) and no evidence of benefit in this group with the best prognosis.[29] The same subgroup has exceptional outcomes on ADT plus ARSIs as observed in the long-term follow-up of ENZAMET (ADT plus enzalutamide, 5-year OS: approximately 85%) versus 65% with TS plus weak NSAA.[16] An update of the STAMPEDE-Abiraterone M1 comparison by disease risk per LATITUDE criteria revealed that the low-risk subgroup (43% of patients) had an estimated 5-year OS of 72% when treated with ADT plus abiraterone.[38] Noting that 95% of participants in STAMPEDE and all patients on LATITUDE have synchronous metastasis, it is reasonable to expect similar outcomes for men with metachronous, low- and high-volume disease treated with abiraterone,[39] as those seen with novel AR inhibitors. This notion was demonstrated one

step earlier in the HSPC continuum in men with high-risk, lymph node–positive M0 prostate cancer treated with RT adjuvant TS plus abiraterone associated with improved OS compared with RT plus TS alone.[40]

DEINTENSIFICATION AND ADAPTIVE APPROACHES

Intermittent and Response-Adjusted Therapy

Many clinicians will have made the observation that there is a subset of patients receiving modern combination therapy, or even ADT alone, that achieve prolonged disease control. Their clinical course is marked by stability of disease symptoms and an undetectable PSA for years. The potential adverse impact of prolonged exposure to these ARSIs remains to be defined, but we do know that abiraterone can exacerbate heart failure and that enzalutamide and apalutamide should not be used with patients at risk for seizure and have been associated with increased falls in the elderly.[41] Indeed, the emergence of treatment-related toxicities may become the dominant clinical priority over time. How do we identify patients suitable for therapy deintensification?

Before the era of combination therapies for mHSPC, deintensification of ADT held a number of proposed benefits. First, progression to castration resistance is adaptive, and replacing androgen levels may therefore prolong the duration of androgen dependence and disease control with AR-directed therapy. Second, intermittent therapy could ameliorate QoL by minimizing adverse symptoms and insidious health effects of continuous castration. SWOG 9346 was a large phase III trial that randomly assigned men with mHSPC to continuous versus intermittent ADT if PSA <4 ng/mL was achieved after 7 months with coprimary end points of difference in QoL at 3 months and OS noninferiority between the arms.[42] After a median follow-up of nearly 10 years, intermittent therapy was not proven to be noninferior for OS, and survival was numerically longer in the continuous arm. Although intermittent therapy resulted in modest improvements in QoL, the lack of definitive OS noninferiority has scuttled widespread adoption of intermittent combined ADT, and clinical practice remains heterogeneous.

Given the apparent stratification of outcomes by baseline clinical factors, there has been increasing interest in identifying response-based end points that may guide not only prognosis but also the development of deintensification strategies for patients with favorable long-term outcomes. PSA is the most thoroughly investigated response end point in this context. SWOG 9346 demonstrated a stratification of outcomes by the level of absolute PSA (PSA ≤0.2 ng/mL, 0.2 ng/mL <PSA ≤4 ng/mL, or PSA >4 ng/mL) after 6-7 months of ADT alone, and a prolonged time to nadir has been associated with even shorter survival in mHSPC.[43-46] Similar stratification of OS by PSA ≤0.2 ng/mL at 7 months was seen in CHAARTED, and this effect remained significant in multivariable analysis adjusting for docetaxel exposure and disease volume.[47] Addition of docetaxel increased the likelihood of PSA suppression (achieved by 37% overall and in a predominately poor prognosis patient population). These data consequently suggest a role for therapy intensification for patients not reaching this PSA milestone on ADT plus docetaxel alone. Similar analyses have been performed in LATITUDE, with 40% of men receiving ADT plus abiraterone who achieved PSA ≤0.1 ng/mL compared with 6.5% on ADT alone.[48] PSA suppression at 6 months correlated with improved rPFS and OS. A preplanned analysis of PEACE-1 showed similar association of rPFS and OS with PSA value measured at 8 months.[49] In ARASENS, addition of darolutamide to ADT plus docetaxel led to a more than doubling of the proportion of patients achieving an undetectable PSA at 24 weeks and 36 weeks, and this correlated with improved OS using either time landmark.[50] In the TITAN trial, achievement of a PSA level of ≤0.2 ng/mL at landmark 3 months of apalutamide therapy was associated with a significantly longer OS (HR, 0.35; 95% CI, 0.25 to 0.48).[51]

Trials combining ADT with ARSIs have a continuous treatment paradigm, which holds several implications. Treatment-related toxicities, effects on health-related QoL, and long-term financial impact need to be considered carefully for all and weighed against efficacy of ARSIs across clinical subgroups—especially in low-volume, metachronous disease where a 90% 5-year prostate cancer–specific survival was noted with TS plus enzalutamide.[16] Moreover, the median OS of control arms across major phase III trials has been consistently improving in the past decade. The SWOG 1216 trial showed a median OS of 70 months in patients treated with ADT plus bicalutamide, twice the value reported in earlier SWOG trials for mHSPC with a similar proportion of patients with extensive disease (visceral metastases and/or presence of at least one bone metastasis beyond the vertebral bodies and pelvis).[52]

Landmark PSA response and other biomarkers may guide treatment de-escalation. The Alliance-sponsored A-DREAM trial (ClinicalTrials.gov identifier: NCT05241860) is a phase II adaptive study where patients receiving ADT plus an ARSI for mHSPC will undergo treatment interruption if PSA <0.2 ng/mL after 18-24 months. Recommencement of therapy will occur on PSA (≥5 ng/mL), radiographic, or clinical progression. The primary end point of the trial is the proportion of men who experience 18-month treatment-free interval (with eugonadal testosterone level) after treatment interruption. EORTC-2238 GUCG (De-Escalate) is a randomized pragmatic trial, sponsored by EORTC, in collaboration with the European Prostate Cancer patient coalition, Europa Uomo, revisiting the concept of intermittent ADT in patients achieving a PSA ≤0.2 ng/mL after 6-12 months of ADT and one of the ARSIs. The study end points include OS, time to next OS-prolonging treatment, health-related QoL,

and resource utilization. In the phase III LIBERTAS trial, men with mHSPC being treated with ADT plus apalutamide and achieving a PSA nadir of ≤0.2 ng/mL within the first 7 months of starting apalutamide will be randomly assigned to continuation of ADT plus apalutamide versus intermittent ADT plus apalutamide. End points include radiographic event-free rate and hot flash severity score and frequency. Novel antiandrogen monotherapy has been tested in an earlier disease setting—for example, enzalutamide without TS in the EMBARK trial (ClinicalTrials.gov identifier: NCT02319837) of biochemically recurrent prostate cancer. Historical data from antiandrogen monotherapy trials suggest lower rates of survival compared with TS.[53] The role of modern noncastrating therapies alone, however, remains undefined.

NOVEL BIOMARKERS AND PRECISION-INFORMED TREATMENT

The answer to guide a new era of therapy modulation and personalization in mHSPC may lie in biology and biomarkers. Much of our knowledge of the biology of mHSPC is derived from deep interrogation of the clinical bookend settings of prostate cancer—localized disease and mCRPC, respectively—over the past 30 years. Large-scale efforts, such as the Cancer Genome Atlas and Stand Up 2 Cancer-Prostate Cancer Foundation program, have provided insights into the genetic, genomic, and transcriptomic landscape of prostate cancer.[54-56]

Although there is a paucity of data to characterize mHSPC specifically, particularly for clinical correlation, recent genomic profiling studies have spurred the need for further investigation. Progression from localized prostate cancer to mCRPC is marked by enrichment of deleterious genomic alterations in the latter disease state. Tumor suppressor genes such *PTEN*, *TP53*, and *RB1* are frequently altered in mCRPC, so too genes that effect DNA damage and repair (*BRCA2*, *BRCA1*, *ATM*, and *FANCA*), PI3K signaling (*PIK3CA* and *AKT1*), chromatin remodeling (*KMT2C* and *KMT2D*), and, most frequently, the *AR*.[57-59] Retrospective data sets reveal that the frequency of such alterations appears to lie between localized prostate cancer and mCRPC, suggesting acquisition of deleterious alterations over time that confers cancer advantage in survival and treatment resistance.[60,61] Interestingly, significant enrichment of such tumor suppressor and *AR* alterations is observed in mCRPC relative to mHSPC (and not mHSPC relative to localized disease). Previous studies have further characterized the mHSPC genomic landscape by clinically relevant groups. High-volume mHSPC has evidence of greater genomic instability measured by global copy number burden and more frequent NOTCH pathway, cell cycle, and Wnt signaling alterations relative to low-volume disease, but no significant differences at an individual gene level.[62,63] Genomic alterations hold prognostic and predictive strength in mHSPC. Tumor sequencing from the STAMPEDE trial has demonstrated a relationship with increasing copy number burden and risk of progression and death in high- and low-volume disease.[64] Time to castration resistance is shorter with alterations in *AR*, *TP53*, *PTEN*, *RB1*, cell cycle, and *MYC* pathways.[61,65] *AR* aberrations detected in circulating tumor DNA (ctDNA) at baseline have been associated with shorter OS.[66] Conversely, *SPOP* mutations are associated with prolonged time to progression and death in patients treated with ARSIs (but not docetaxel) for mHSPC.[67,68]

Prognostic transcriptomic biomarkers are established in localized prostate cancer to the point of clinical implementation.[69,70] The role of such assays in advanced disease is not well-defined; however, recent RNA profiling of mHSPC suggests strong biomarker potential. Profiling of 160 patients from CHAARTED using the Decipher microarray platform was the first to comprehensively map the transcriptomic landscape of mHSPC.[71] Applying discrete signatures, marked differences were noted compared with localized prostate cancer with predominance of luminal B and basal subtypes (and <5% with luminal A), lower AR activity, and enrichment for high Decipher risk. When translated to outcomes, luminal B subtype was associated with poorer prognosis on ADT but significantly benefited from addition of docetaxel (and no significant benefit for docetaxel was seen in the basal subtype). Higher Decipher risk and lower AR activity were associated with shorter OS, and this effect remained significant despite adjusting for disease volume and metastatic timing. These data propose both prognostic and predictive roles for transcriptional subtyping in mHSPC. Comparative data from TITAN demonstrated similar enrichment of adverse-risk subtypes and their association with shorter rPFS. However, there was evidence of benefit for adding apalutamide to ADT across molecular subtypes.[72] Similar findings support the prognostic role of Decipher risk as reported in a STAMPEDE cohort treated with ADT with or without abiraterone.[73] The beneficial effect of abiraterone was noted across subtypes, mirroring the benefit of ARSIs across clinical subgroups (in contrast to docetaxel). Put together, transcriptomic profiling of mHSPC has revealed a molecular landscape skewed toward known aggressive and poor prognosis subtypes. Evidently transcriptomic subtyping can provide prognostic information independent of clinical factors. Its role as a predictive biomarker requires further development, validation, and aggregate analysis across data sets.

We are now getting closer to testing the potential benefits of biomarker-informed clinical trials of precision therapy for mHSPC (Table 2). The expansion of understanding personalized and targeted treatments in mCRPC is ripe for investigation in mHSPC, promising greater balance in the

TABLE 2. Selected Registration Phase III Trials in the Metastatic Hormone-Sensitive Prostate Cancer Setting

Trial	Phase	Target Enrollment	Inclusion Criteria	Previous Docetaxel Therapy in the Metastatic Hormone-Sensitive Setting	Intervention Arm	Control Arm	Primary End Point
PSMAddition (NCT04720157)	III	1,126	PSMA-positive disease on a ^{68}Ga-PSMA-11 PET/CT scan Treatment-naïve or up to 45 days of ADT before inclusion or up to 45 days of ARSI	Not allowed	^{177}Lu-PSMA-617 intravenously once every 6 weeks for six cycles plus standard of care (ADT plus ARSI)	Standard of care (ADT plus ARSI)	rPFS
AMPLITUDE (NCT04497844)	III	788	Positive for deleterious germline or somatic homologous recombination repair gene mutations Ongoing ADT Radiation with curative intent or previous treatment with PARPi not allowed Up to 6 months of ADT or 45 days of abiraterone acetate and prednisone allowed before random assignment	Allowed	Niraparib 200 mg orally once daily plus abiraterone acetate 1,000 mg orally once daily plus prednisone 5 mg orally once daily	Placebo plus abiraterone acetate 1,000 mg once daily plus prednisone 5 mg once daily	rPFS
TALAPRO-3 (NCT04821622)	III	550	Positive for deleterious germline or somatic homologous recombination repair gene mutations Ongoing ADT Previous docetaxel for mHSPC or previous treatment with a PARPi not allowed ≤3 months of ADT with or without ARSI for mHSPC allowed before random assignment	Not allowed	Talazoparib 0.5 mg orally once daily plus open-label enzalutamide 160 mg orally once daily	Placebo plus open-label enzalutamide 160 mg orally once daily	rPFS
CAPItello-281 (NCT04493853)	III	1,000	Synchronous mHSPC PTEN deficiency on tissue immunohistochemistry Ongoing ADT Previous surgery or radiation with curative intent not allowed	Not allowed within 3 weeks of first dose of study treatment	Capivasertib 400 mg orally twice daily (intermittent weekly dosing schedule) plus abiraterone acetate 1,000 mg orally once daily	Placebo plus abiraterone acetate 1,000 mg orally once daily	rPFS
CYCLONE-03 (NCT05288166)	III	900	High-risk mHSPC (≥4 bone metastases and/or ≥1 visceral metastasis) Ongoing ADT Previous systemic treatment for metastatic prostate cancer not allowed except ADT with or without ARSI up to 3 months before random assignment	Allowed	Abemaciclib plus abiraterone acetate plus prednisone	Placebo plus abiraterone acetate plus prednisone	rPFS
KEYNOTE-991 (NCT04191096)	III	1,232	Previous treatment with an ARSI or immune checkpoint inhibitor not allowed Ongoing ADT Up to six previous cycles of docetaxel allowed without evidence of progression Absence of a superscan bone scan	Allowed	Pembrolizumab 200 mg intravenously once every 3 weeks plus enzalutamide 160 mg orally once daily	Placebo plus enzalutamide 160 mg orally once daily	rPFS OS

Abbreviations: ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor; PET, positron emission tomography; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival.

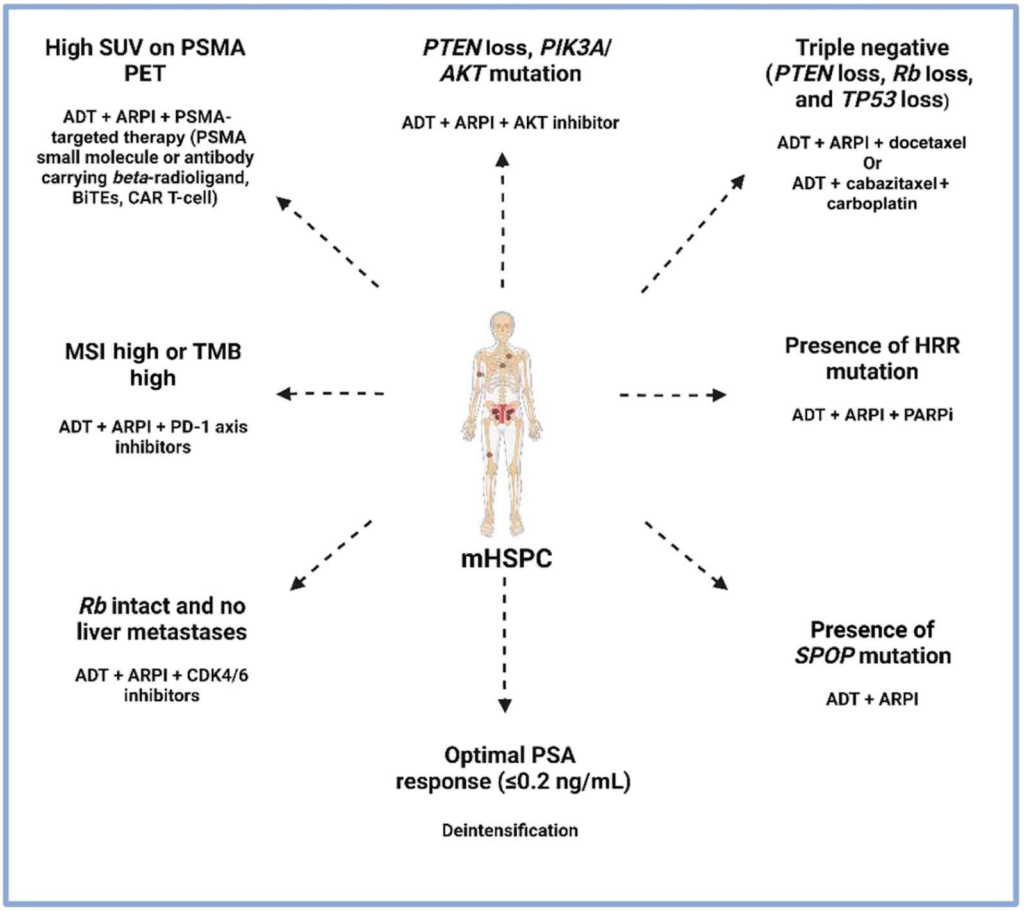

FIG 2. Potential precision therapy approaches in mHSPC. ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BiTEs, bispecific T-cell engager; CAR T cell, chimeric antigen receptor T cell; CDK4/6, cyclin D Kinase 4/6; HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer; MSI, microsatellite instability; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed cell death protein 1; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; TMB, tumor mutational burden.

benefit to burden ratio of systemic therapies (Fig 2). The frequency of germline and somatic BRCA1/2 and homologous recombination–associated gene alterations in metastatic prostate cancer and the success of poly (ADP-ribose) polymerase (PARP) inhibitors in this context[74] have led to the development of numerous trials or PARP inhibitor combinations in mHSPC. Targeting frequent PI3K-Akt pathway alterations and cell cycle dysregulation in mCRPC[75,76] has spurred study in the hormone-sensitive setting, combining AKT inhibitors and CDK4/6 inhibitors with hormonal therapy, respectively. ^{177}Lu-PSMA-617 has received FDA approval for the treatment of mCRPC on the basis of significant activity[77] and OS improvement.[78] As a form of molecular-targeted therapy using novel PET imaging, ^{177}Lu-PSMA-617 holds promise in mHSPC because of the widespread expression of PSMA in hormone-sensitive disease. Trials combining ^{177}Lu-PSMA-617 with chemotherapy (eg, UpFrontPSMA, NCT04343885) or ARSI (eg, PSMAddition, NCT04720157) are ongoing. The rapid development of predictive biomarkers is directly influencing the design of future multiarm umbrella trials in mHSPC, guided by baseline and on-treatment molecular, PSA, and imaging characterization and other levels of individual data to define treatment strategies.

CONCLUSIONS

Rapid shifts in the paradigm and complexity of therapy for mHSPC in recent years have led to significant improvement in OS, especially notable for those with synchronous, high-volume disease associated with worse prognosis, converting mHSPC from imminently deadly to a disease with the ultimate goal of durable control. Contemporary data from mHSPC clinical trials highlight notable improvements in the prognosis of patients across the spectrum of risk, and these need to be adopted and realized in the real world. However, many unanswered questions remain. Men are living longer with metastatic prostate cancer, and it remains imperative that new treatment approaches promote personalization to increase patient benefit and decrease the unbalanced burden.

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